

reinforce the aim of this Scientific Opinion. In addition, some considerations on epidemiology have been tone-down. The toxicological studies are not within the terms of reference of this opinion but uncertainty in the form of assessment factors are a regular part of the Risk Assessment based on toxicology studies for MRL setting is a current example.

- Mechanistic. The authors tend to favor ranking, pooling, and other methods that summarize diverse quality literature, rather than a integrated assessment of existing knowledge. They assume that there is a large number of equivalent studies that can be summarized quantitatively. They prefer experimental model where standardized repeated studies could be done, or with the clinical trials from where meta-analysis originated.

EFSA Response:

The use of toxicological evidence in risk assessment of pesticides is the current practice according to EU regulation. The current opinion is also proposing a methodology for the integration of all the available reliable evidence (epidemiological included) by using a weight of evidence approach. Please see chapter 7.2.

- Missing considerations: The authors do not advocate for the necessary substantial ongoing stream of funding for surveillance and post-marketing surveillance of pesticides that could strengthen our capacity to identify real life events, nor for expanded, diversified, well-funded, and more detailed epidemiologic studies being now concentrated in just some centers and labs.

EFSA Response:

The PPR Panel was surprised of such comment, since this was part of Chapter 6. No amendment of the Opinion is required.

- Vulnerability of study populations: The authors do not provide any input on the strength of epidemiology not only to examine real life conditions of exposure and disease, but also to assess how these exposures and effects can happen in vulnerable populations, that are not standardized as in during the in vivo experiments, e.g. for migrants or when pesticides are used worldwide under diverse ecological conditions.

EFSA Response:

This comment is beyond the scope of the Opinion and vulnerable subpopulations are taken into consideration in chapter 2.

- Missed outcomes. The authors miss the real life outcomes that can happen and are seldom observed in vivo, or even discarded. Such is the case of in vivo studies where congenital anomalies are overlooked, discarded or grossly classified, and then appear in real human population situations. Much of the literature is driven by studies in mammals and other species, where these in vivo studies seldom resemble human exposure pre-conceptionally or during the critical window of organogenesis. The number of relevant epi studies is small specially for non-cancer outcomes. Much of the comments by the authors overlook the need for complete in vivo studies to examine very short and very long term effects (with complete life course follow up of animals).

				<p>Exposome and cumulative risk assessment can be used improperly to ignore the individual responsibility of a chemical. Retrospective exposure assessment and biomonitoring is not adequately covered by the authors. We do not agree that epidemiology cannot be used for hazard assessment: it is self-evident from the practice of surveillance and case-control studies. The SWOT analysis downplays the internal factors (SW) and overemphasizes the external ones (OT), highlighting the lack of insight on the epidemiologic practice on the part of the authors.</p> <p><i>EFSA Response:</i> <i>These comments are considered meaningful but fall outside the aim of this document, which was focused on epidemiology only. The PPR Panel does state the advantage of epidemiology over animal studies in that the animal studies could have other mechanisms etc. Also the PPR Panel does highlight (and can further emphasize) the potential of epidemiology for hazard identification.</i></p> <p>We suggest a balanced panel, addressing the overall production of pesticide science, aiming to enhance the integration and advancement of knowledge. We urge EFSA to develop and apply standardized protocols for risk assessment rather than ask each panel to improvise and produce position papers on issues that are not within their area of knowledge as is the case with the pesticides paper.</p> <p><i>EFSA Response:</i> <i>The work group membership had a majority of epidemiologists and access to advice from external experts with expertise in epidemiology. The comment about hazard "assessment" is a misunderstanding of the distinction drawn in the Risk Assessment between Hazard identification and Hazard characterisation. The conclusion in general terms was that epidemiology was already helpful for the former but will need specific improvements in areas such as exposure assessment to maximise its potential for risk assessment of pesticides. Finally, it's important to highlight that this document is a Scientific Opinion and not a Guidance. A Guidance on this issue will probably follow immediately after.</i></p>
122	Centre F Baclesse	FRA	4.3 Study populations	<p>1255-1257: It would seem to me that a threshold even for individuals in "a preclinical state" would be important to know. Could this not be considered a "vulnerable subpopulation" ?</p> <p><i>EFSA Response:</i> <i>The possibility that individuals in a "preclinical state" can be considered as a vulnerable subpopulation is implicitly assumed in lines 1256-57 where it is claimed that people in a preclinical state would be sensitive to the low end of the dose-response curve. However, this interpretation is beyond the usual concept of vulnerable subpopulations.</i></p>
123	Université de Bordeaux	FRA	4.3 Study populations	<p>1255-1257: It would seem to me that a threshold even for individuals in "a preclinical state" would be important to know. Could this not be considered a "vulnerable subpopulation"?</p> <p><i>EFSA Response:</i> <i>Same text as comment #122.</i></p>

124	Defra Expert Committee on Pesticides on behalf of the Health & Safety Executive	GBR	4.3 Study populations	<p>If (human) response heterogeneity is expected then a more detailed stratification may be needed; for example, incorporating geographic distribution, and 'ethnicity' as well as age and sex/gender. There are likely other known sources of genetic variation too.</p> <p><i>EFSA Response:</i> <i>The PPR Panel agrees with this comment. It has been incorporated into the Scientific Opinion. Text in line 1247 has been amended as following: "...key population characteristics (e.g. sex, age, geographic distribution, ethnicity, or genetic variation)".</i></p>
125	Defra Expert Committee on Pesticides on behalf of the Health & Safety Executive	GBR	4.4 Improvement of exposure assessment	<p>4.4b GIS is useful but since exposure from application in agricultural fields will be influenced by wind direction, amongst other factors, as well as proximity data would be improved by taking this into account. It follows that a spatial analysis of outcomes is a necessary precursor to make best use of this approach.</p> <p><i>EFSA Response:</i> <i>The PPR Panel agrees for airborne residues exposure might be influenced by wind direction, but some exposures maybe a result of entry into treated area (perhaps unauthorised but also on public paths) and the dermal route maybe more important.</i> <i>The following sentence has been included in line 1405: "As some such exposures maybe influenced by wind direction, amongst other factors, this should be taken into account through a special analysis of outcomes to make best of use of the approach. "</i></p>
126	ECPA	BEL	4.4 Improvement of exposure assessment	<p>Line 1317-1321: "Failure to use these existing methods restricts the potential for the use of epidemiological evidence in the regulation of specific pesticides. It is therefore important that those contemplating future studies carefully consider approaches to be used to avoid misclassification of exposure, and to conduct appropriate detailed exposure assessments for specific pesticides, which allow for sound dose-response analyses, and demonstrate the validity of the methods used". Some considerations for ensuring sound and reliable exposure assessment are incorporated in the guidelines provided in Appendix A of our comments. We would encourage the PPR Panel to consider these points and to fully incorporate the specific guidance for robust exposure assessment of short-lived pesticides discussed in LaKind et al. (2014). The scientific opinion should also discuss whether it is feasible for future epidemiology studies to incorporate all these methods and if not, how future studies can or should be used in risk assessments. Clarification of recommendations will assist future investigators when seeking funding to justify high quality and more costly method(s).</p> <p>In section 4.4 the PPR Panel discuss the use of personal exposure monitors that are specific to pesticide exposure (e.g. sensors to measure airborne concentrations, "skin" patches to measure dermal concentrations, or real time data transfers via mobile phones) in order to improve exposure assessment at the personal level. Important data protection issues and ethical considerations are acknowledged by the Panel. There are however further critical points which should be taken into account. The use of these devices and the (potentially) continuous inflow of real-time big data can pose some organizational, statistical, technical and personnel challenges. Furthermore, since many studies require long follow-up times, the amount and processing of data becomes even more complicated. As the Panel correctly notes in section 7.7 "...there are challenges to find relevant signals in potential oceans of noise".</p>

				<p>Line 1308: "Validated confirmatory methods shall be submitted if appropriate". Validated confirmatory methods (i.e., the reproducibility of the method shall be determined by means of an independent laboratory validation and reported) should also be included as one of study quality criteria to avoid misclassification of exposure and to allow sound dose response analysis.</p> <p><i>EFSA Response:</i> <i>The method proposed by Lakind has been taken into consideration in regards to the assessment of the quality of the epidemiological studies under chapter 4.1 (see also #114).</i> <i>Regarding the use of personal exposure monitors that are specific to pesticide exposure, the PPR Panel agrees that the generation of huge volumes of data can pose organisational, statistical, and technical challenges, particularly with extended follow-up times.</i></p>
127	ECPA	BEL	4.4 Improvement of exposure assessment	<p>Line 1356: What is meant by "cost and precision"? The cost of HBM analyses is not discussed and weighted in the scientific opinion. It is therefore difficult to rate HBM costs against other 'hard input' such as medical examination data or environmental analyses. Does "precision" mean "analytical imprecision" or "variability of biomarkers"?</p> <p><i>EFSA Response:</i> <i>The external HBM report (see Appendix B of the Opinion and the External Scientific Report) discusses some strengths and weaknesses. The latter include inability to distinguish routes into body, may be invasive (blood), may monitor metabolites rather than toxic compounds of interest, for compounds in urine there maybe uncertainty regarding variation in hydration, often a lack of human PBPK data, where human data are available these are likely to be based on extremely small scale studies, development and validation of methods may be expensive, there may be issues of potential confounding exposures from other sources. Line 1368 change: "... changes that occur at environmentally relevant exposure concentrations ..." to "... changes in exposure that occur at environmentally relevant concentrations ..."</i></p> <p>Line 1368: What is meant by "changes"? Does this refer to health outcome or exposure level?</p> <p><i>EFSA Response:</i> <i>This refers to exposure level and it has been amended in the text accordingly.</i></p> <p>Line 1372: It is not clear how PBPK/TK models can improve the validity of HBM data or of the conclusions drawn from HBM results. Toxicologically-derived HBM assessment values (not reference values) already account for tissue distribution and target concentrations. Can the PPR Panel clarify what is meant by the statement "PBPK models need to be validated" (line 1380/81)? Against which validation criteria?</p>

EFSA Response:

It is not suggested that PBPK can improve the validity of HBM, but it can improve the understanding of the relationship between BM levels and dose.

A discussion of the evaluation of PBPK models which would include demonstration of: representative life-stages; adequate structure and parameters; simulation over appropriate time courses of concentrations of pesticides and/or metabolites in relevant compartments, tissues or organs following relevant routes of exposure, is beyond the scope of this opinion.

Line 1387: "Larger epidemiological studies". Which kind of epidemiology studies is this referring to, prospective or retrospective studies?

EFSA Response:

The type of study foremost in mind here is prospective, but there are possibilities here for retrospective studies, too.

Line 1401-1405: Regarding geographical information systems and exposure. Additional discussion of validation of these approaches is recommended. This is particularly relevant for the specific characteristics which will vary for specific pesticides, formulations and moieties, which will in kind, result in different residential exposures attributed to drift.

EFSA Response:

Additional discussion of validation of these approaches is beyond the remit of the opinion.

Line 1406: What is the purpose and additional value of non-specific (complementary) tools if exposure to chemicals, confirmed by HBM, is linked to health outcomes? The PPR Panel adds "when validated" (line 1404) but what does that mean for study design and interpretation? What are appropriate validation criteria?

EFSA Response:

The challenges of HBM in constructing long term exposure histories for compounds with short biological half-lives is discussed elsewhere, assuming that repeated biological sampling is not practicable the complimentary application of other technologies supported or calibrated by HBM studies may reduce the uncertainties within the overall exposure assessment, similar to approach in the AHS.

Line 1409-1419: Further clarification would be helpful on how to use omics technologies for the purposes of exposure assessment and how to interpret the resulting data.

EFSA Response:

The text here indicates that these are intriguing possibilities, and the HBM report indicates that this is an early area of research, particularly for pesticides. There are obvious technical issues to consider such as reproducible quantitation, quality assurance, and handling very large datasets, but these issues are the scope of the Terms of